REMARKS

Status of the Claims

Claims 1-44 were withdrawn from consideration and are now canceled. Claims 45-82 are pending. Claims 45-57 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the written description requirement. Claims 45-48, 54-59, 61-65, 70, and 71 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Gaster *et al.*, U.S. Patent No. 6,235,758. Claims 45-57 stand rejected under the judicially created obviousness-type double patenting as allegedly unpatentable over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349. Claims 45-82 stand rejected under the judicially created obviousness-type double patenting as allegedly unpatentable over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349 in view of Gaster *et al.*, U.S. Patent No. 6,235,758.

The Invention

Applicants have demonstrated for the first time that openers of KCNQ potassium channels alleviate anxiety. The mechanism for treating anxiety by opening KCNQ potassium channels was previously unknown. Applicants have demonstrated the efficacy of this discovery using an *in vivo* experimental procedure routinely used by the pharmaceutical industry to screen for and identify drugs effective for the treatment of generalized anxiety disorder. The present application therefore provides not only a mechanism for treating anxiety disorders, but also a large number of structurally diverse compounds that open KCNQ potassium channels as well as assays for identifying compounds that open KCNQ potassium channels and reduce anxiety.

Rejections under 25 U.S.C. §112, first paragraph

Introduction

Claims 45-57 stand rejected as allegedly containing subject matter that was not described in the specification as originally filed. The Examiner asserts that the phrase "a compound able to increase ion flow through KCNQ potassium channels" is not adequately described because the specification does not present structural identifying characteristics for this

component other than the N-aryl benzylamide compounds of Figure 7. Applicants respectfully traverse this rejection because the specification sets forth:

(1) A novel mechanism for treating anxiety by increasing ion flow through KCNQ potassium channels;

(2) A large number of structurally diverse compounds able to increase ion flow through KCNQ potassium channels;

(3) Assays to determine the ability of channel openers to treat anxiety; and

(4) A working example of the invention as claimed.

The Law Regarding Fulfillment of the Written Description Requirement

There are situations where an applicant can properly obtain method claims to medical treatments based on the administration of chemical agents that are defined solely by function without structure. See *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63USPQ2d 1609, 1613 (Fed. Cir. 2002), stating "[i]t is not correct . . . that all functional descriptions of genetic material fail to meet the written description requirement." In *Enzo*, the United States Court of Appeals for the Federal Circuit held that the written description requirement for functional claim descriptions is satisfied when the functional characteristics are coupled with a disclosed correlation between that function and a structure that is "sufficiently known or disclosed." *Id.* The court explained that if the disclosed compounds "are representative of the genus claims, *i.e.*, if they indicate that the patentee has invented species sufficient to constitute the genera, they may be representative of the scope of the claims." *Id.* at 1615.

The patent at issue in *Enzo* was directed to nucleic acid sequences that preferentially hybridize to the chromosomal DNA of *Neisseria gonorrhea* over *Neisseria meningitidis*. The patentee disclosed only ***three*** operative nucleic acid sequences which hybridized to only ***six*** strains of *Neisseria gonorrhea*. The patentee sued two of its competitors for infringement, and the defendants moved for summary judgment on the ground that the claims were invalid for failure to meet the written-description requirement. The district court granted the motion, concluding that the claimed composition of matter was defined only by its biological

function, which it deemed insufficient to satisfy § 112, P 1. The Federal Circuit reversed summary judgment, finding that genuine issues of material fact existed regarding satisfaction of the written-description requirement. Thus, the Federal Circuit refused to uphold summary judgment under § 112, P 1 invalidating a claim for functionally describing ***all*** nucleic acid probes that bind to ***any*** strain of *Neisseria gonorrhea* where the specification set forth only ***three*** operative nucleic acid probes that hybridize to only ***six*** strains of *Neisseria gonorrhea*.

In reversing the district court, the Federal Circuit in *Enzo* distinguished its earlier decision in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). In *Lilly*, the Federal Circuit determined that a disclosure of a ***single*** rat cDNA was not descriptive of a broad claim encompassing mammalian and vertebrate cDNA. See *Enzo* at 1615, citing *Lilly* at 1405. The *Enzo* court pointed out that, in *Lilly*, the specification of the patent at issue failed to "describe a sufficient number of species within the very broad genus to indicate that the inventors had made a generic invention, i.e., that they had possession of the breadth of the genus, as opposed to merely one or two such species." See *Enzo* at 1615.

Therefore, according to the Federal Circuit, disclosure of ***three*** nucleic acid sequences that preferentially hybridize to **six** strains of *Neisseria gonorrhea* may be a sufficient correlation between structure and function to claim ***all*** nucleic acid sequences that preferentially bind to ***any*** strain of *Neisseria gonorrhea*. However, disclosure of a ***single*** rat cDNA is not sufficient to claim a genus of compounds encompassing mammalian and vertebrate cDNA.

In *University of Rochester v. G.D. Searle & Co.*, the U.S. District Court for the Western District of New York applied the guidelines relating to nucleic acid composition claims set forth by the Federal Circuit in *Enzo* and *Lilly* to claims covering a method of selectively inhibiting an enzyme using a pharmaceutical agent. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (W.D.N.Y. 2003). The patent at issue claimed a "method for selectively inhibiting PGHS-2 [mammalian prostaglandin H synthase-1] activity in a human host" using a "non-steroidal compound" in which "the activity of PGHS-1 is not inhibited." See *Rochester* at 1426.

The district court repeated the standard set forth by the Federal Circuit in *Enzo*, stating "the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics,' including, *inter alia*, 'functional characteristics when coupled with a known or disclosed correlation between function ad structure.'" *Id.* at 4129. However, because the specification did not set forth "so much as one compound that would be suitable for use in practicing the claimed invention," the district court granted summary judgment invalidating the claims for failing to fulfill the written description requirement. *Id.* at 1431. The Federal Circuit has recently upheld the district court's decision in *Rochester*. See *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004). The court reaffirmed that the written description is a separate requirement, which applies to all types of inventions, including non-genetic materials and method claims. *Id.* at 1891, 183.

It is apparent from *Enzo*, *Lilly*, and *Rochester* that an applicant can properly obtain method of treatment claims based on the administration of chemical agents defined solely by function. To obtain such claims, the specification should correlate that function with a structure that is "sufficiently known or disclosed." According to the Federal Circuit, the required correlation between structure and function may be met by disclosing as few as ***three*** operable structures. *Id* at 1613.

Applicants respectfully assert that, in light of the Federal Court decisions outlined above, the large number of structurally diverse compounds disclosed in the current specification is more than adequate to meet the structure-function correlation standard set forth by the Federal Circuit. Moreover, Applicants have also disclosed a novel mechanism for treating anxiety by increasing ion flow through KCNQ potassium channels, assays to determine the ability of channel openers to treat anxiety, and a working example.

In addition to the case law outlined above, the Examiner is respectfully reminded that to fulfill the written description requirement, a patent specification must merely describe a method in sufficient detail that one skilled in the art can reasonably conclude that the inventor was in possession of the claimed method. See *Lockwood v. American Airlines, Inc.*, 41 USPQ2d 1961, 1966 (1997); *Vas Cath, Inc. v. Mazurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991). A

specification may provide support in a variety of ways, including the disclosure of a working embodiment that meets all of the limitations of the claim. See *Cooper v. Goldfarb*, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998). Furthermore, the Examiner "has the initial burden of presenting evidence or reasons why persons of skilled in the art would not recognize in the disclosure a description of the invention defined by the claims." See *In re Wertheim*, 191 USPQ 90, 97 (CCPA 1976). Therefore, where the specification provides an actual reduction to practice of a process that meets all the limitations of the claim thereby demonstrating that the invention works for its intended purpose, the Examiner must present evidence as to why one skilled in the art would not reasonably conclude that the inventor was in possession of the claimed method. See MPEP §2163 II.A.3.(a).

The specification sets forth a novel mechanism for treating anxiety by increasing ion flow through KCNQ potassium channels

The point of novelty of the present invention lies in the discovery of a new mechanism of treating anxiety by increasing ion flow through KCNQ potassium channels. This novel mechanism is repeatedly disclosed throughout the specification, for example, at page 3, lines 14-20; page 3, lines 23-25, page 3 line 32 to page 4, line 4; page 12, line 4 to page 6, line 13; and Example 6. Applicants respectfully assert that the disclosure of this novel mechanism, coupled with the extensive teachings set forth in the specification as outlined below, satisfies the legal requirements for obtaining method claims to anxiety treatments based on the administration of chemical agents that are defined solely by their function as KCNQ channel openers, without structure.

The specification sets forth large number of structurally diverse compounds able to increase ion flow through KCNQ potassium channels

The Examiner states that "[t]here is no evidence that there is any per se structure/function relationship between the phrase, 'a compound able to increase ion flow through KCNQ potassium channel' other than those disclosed, namely the N-aryl benzylamide compounds of Figure 7." See page 3, lines 4-6 of Examiner's Office Action mailed September 26, 2003. Apparently, the Examiner asserts that claims 45-57 should be limited to the N-aryl

benzylamide compounds of Figure 7 because these are the only disclosed KCNQ channel opening compounds. Applicants respectfully disagree.

The specification sets forth a large number of structurally diverse KCNQ channel openers representative of the scope of the claims. For example, the specification discloses a structurally diverse genus of KCNQ channel openers able to increase ion flow through KCNQ potassium channels. See page 4, line 29 to page 9, line 19.

Furthermore, contrary to the Examiner's assertion, Figure 7 sets forth a list of exemplary KCNQ channel openers much more diverse than N-aryl benzylamides. The following exemplary KCNQ channel openers are disclosed in Figure 7:

N-aryl oxazole amides;
N-aryl furan amides;
N-aryl thiazole amides;
N-aryl thiadiazole amides;
N-aryl isothioazole amides;
N-aryl imidazole amides;
N-aryl pyrazole amides;
N-aryl triazole amides;
N-aryl thiophene amides;
N-aryl indole amides;
N-aryl purine amides;
N-aryl benzoimidazole amides;
N-aryl benzofurane amides;
N-aryl benzothiophene amides;
N-aryl benzoisothiazole amides; and
N-aryl benzylamides.

In addition to the KCNQ channel openers set forth in Figure 7, the specification also discloses a diverse array of KCNQ channel openers set forth in USSN 60/158,712, filed October 8, 1999, from which the current application claims priority. USSN 60/158,712 discloses

a variety of N-aryl, N-alkyl, and N-cycloalkyl pyrazole amide KCNQ channel openers. For purposes of convenience, the compounds set forth in USSN 60/158,712 are attached to this Response as Exhibit No. 1.

In light of *Enzo*, where the Federal Circuit determined that the required correlation between structure and function may be met by disclosing as few as ***three*** operable structures, the presently disclosed array of structurally diverse compounds would appear to be more than adequate to meet the required correlation between structure and function. Yet, the Examiner has apparently taken the position that Applicants' extensive disclosure and exemplary compound lists are not enough to satisfy the standard set forth by the Federal Circuit. If the Examiner's position were correct, then method claims based on the administration of chemical agents defined solely by function without structure would likely never issue. However, a number of such claims have issued from the United States Patent Office.

Applicants' attorney conducted a computer search for claims reciting medical methods where the methods require the use of pharmaceutical compounds defined entirely by function rather than by structure. There were many examples and a summary list of patents with exemplary claims are attached to this Response as Exhibit No. 2. For purposes of convenience, copies of the actual patents are attached to this Response as Exhibit No. 3. The Examiner is invited to review the summary list with exemplary claims and the actual patents. A cursory review of the patents reveals that the correlation between structure and function provided in the subject application greatly exceeds that disclosed in these thirty-one patents.

Disclosure of Assays to Identify KCNQ Channel Openers

In addition to the large number of structurally diverse KCNQ channel openers, the specification sets forth a number of assays to identify KCNQ channel openers. The assays involve the *in vivo* or *in vitro* treatment of a sample containing a KCNQ channel with a potential KCNQ channel opener and subsequent measurement of the KCNQ potassium channel activity. See page 23, lines 25-29. The activity of the test compound may then be compared with untreated control samples. See page 23, lines 27-29.

KCNQ potassium channel opening activity may be determined by measuring changes in ion flux through detection of cell or membrane polarization. See page 24, lines 4-6. Cell or membrane polarization is detected by measuring changes in current using standard techniques such as voltage clamps or patch clamps. See page 24, lines 6-10.

Other standard assays for measuring ion flux are also disclosed, such as those involving the measurement of potassium or rubidium ions flux by directly detecting the concentration changes of the ions (e.g., radioisotopic labeling). See page 24, lines 23-32. In addition, ion flux may be measured by determining changes in physiological conditions, such as transmitter release (e.g., dopamine), hormone release (e.g., insulin), transcriptional changes to both known and uncharacterized genetic markers (e.g., northern blots), cell volume changes (e.g., in red blood cells), immunoresponses (e.g., T cell activation), changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as Ca^{2+}, or cyclic nucleotides. See page 24, line 30 to page 25, line 8.

At page 23, lines 12-18, the specification further provides an array of methods useful in identifying KCNQ channel openers, including:

> measuring current; measuring membrane potential; measuring ion flux; e.g., potassium or rubidium; measuring potassium concentration; measuring second messengers and transcription levels, using potassium-dependent yeast growth assays; measuring pain responses in mice, e.g., with formalin algesia or hotplate assays; measuring ligand binding; and using, e.g., voltage-sensitive dyes, radioactive tracers, and patch-clamp electrophysiology.

Moreover, the assays set forth in the specification were well known in the art at the time of filing the application. The fact that these methods were well known in the art is supported by the references cited in the specification, such as:

Ackerman *et al., New Engl. J. Med.* 336:1575-1595 (1997);

Hamil *et al., Pflugers. Archiv.* 391:85 (1981);

Vestergarrd-Bogind *et al., J. Membrane Biol.* 88:67-75 (1988);

Daniel *et al., J. Pharmacol. Meth.* 25:185-193 (1991);

Holevinsky *et al., J. Membrane Biology* 137:59-70 (1994);

Blatz *et al., Nature* 323:718-720 (1986); and

Park, *J. Physiol.* 481:555-570 (1994).

The Examiner has presented no evidence or reasoning as to why one skilled in the art would doubt the usefulness of the functional assays disclosed in the specification or well known in the art. Therefore, after examining the assays set forth in the specification and reviewing assays well known in the art, one skilled in the art would conclude that Applicants were in possession of standard methods for identifying potassium channel openers.

Disclosure of Assays to Determine the Ability of Channel Openers to Treat Anxiety

The specification also sets forth assays to test potassium channel openers for their ability of treat anxiety. On page 12, line 16 to page 13, line 3, the specification provides a detailed description of assays useful in testing anxiolytic effects:

> The standard test in rat to measure anxiolytic effect (Geller conflict procedure) was designed by Geller and Seifter and modified by Pollard and Howard (Geller & Seifter, *Psychophamracologia* 1:482-492 (1960: Pollard & Howard, *Psychopharmacology* 62:117-121 (1979)). The anxiety-reducing effect of a KCNQ2/3 channel opener was measured using the Geller conflict procedure in rats. Rats are trained to press a lever to receive food pellets during daily 1 hour sessions. The sessions are divided into punished and unpunished phases. During the four, three-minute punished periods, a light signals that each lever press will produce both a pellet and a foot shock (punishment), which reduces lever pressing. The number of punished lever presses on test days (when test compound is administered) is compared to the mean on baseline days. The positive control, chlordiazepoxide, increases punished lever pressing by > 50%. A compound that produces an increase of approximately 40% or greater is generally considered to be of interest as a rapid-onset anxiolytic. A selective KCNQ2/3 channel opener increased punished responding in a dose dependent, statistically significant manner (Figure 6).

Again, these assays are well known in the art, as evidenced by the multiple citations in the above passage. The Examiner has not questioned the validity of these methods or provided reasoning as to why one skilled in the art would doubt the usefulness of the disclosed assays. Thus, Applicants assert that one skilled in the art, using the teachings in the specification and methods generally known in the art, would be able to determine the ability of KCNQ channel openers to treat anxiety in a subject. Absent some reasoning or evidence to doubt the usefulness of the methods disclosed in the specification, Applicants submit that one skilled in the art would recognize that Applicants were in possession of a method of identifying a KCNQ potassium channel opener useful in treating anxiety.

Disclosure of a Working Example

As mentioned above, a specification may provide support by including the disclosure of a working embodiment that meets all of the limitations of the claim. See *Coope* at 1901. Furthermore, where the specification provides an actual reduction to practice of a process that meets all the limitations of the claim thereby demonstrating that the invention works for its intended purpose, the Examiner must present evidence as to why one skilled in the art would not reasonably conclude that the inventor was in possession of the claimed method. See MPEP §2163 II.A.3.(a).

The specification provides a working example of the claimed invention in which a KCNQ channel opener is administered in accordance with the protocol of the Geller conflict model. See Example 6. This example demonstrates that the invention as claimed works for its intended purpose. The Examiner has presented no evidence or reasoning as to why one skilled in the art would doubt the validity of this experiment. Moreover, the Examiner has presented no evidence or reasoning as to why one skilled in the art, after examining this experiment, would conclude that a KCNQ channel opener would ***not*** work as intended in claims 45-57.

Therefore, Applicants respectfully submit that one skilled in the art would recognize that Applicants were in possession of a method of reducing anxiety using a compound that increases ion flow through a KCNQ potassium channel as claimed.

Summary of Applicants' Disclosure

In sum, Applicants' disclosure sets forth:

(a) A novel mechanism for treating anxiety by increasing ion flow through KCNQ potassium channels;

(b) A large number of structurally diverse compounds capable of increasing ion flow through KCNQ potassium channels;

(c) Methods to identify KCNQ channel openers;

(d) Methods to test KCNQ channel openers for their ability to treat anxiety; and

(e) A working example of the claimed invention.

Therefore, one skilled in the art would necessarily conclude that Applicants discovered a method for treating anxiety using ***any*** KCNQ channel opening compound regardless of the actual structure of the KCNQ channel opener. In light of the disclosure outlined above, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §103(a)

Claims 45-48, 54-59, 61-65, 70, and 71 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Gaster *et al.*, U.S. Patent No. 6,235,758 (hereinafter referred to as "Gaster"). The Examiner asserts that Applicants' invention merely elucidates a mechanistic step that is inherent in the administration of the aryl carbamoyl compounds of Gaster. The Examiner reasons that because this mechanistic step is inherent in the aryl carbamoyl compounds of Gaster, it would have been obvious for one skilled in the art to treat anxiety as claimed.

Burden of Proof in Establishing Prima Facie Obviousness

"The examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if this burden is met does the burden of coming forward with rebuttal arguments or evidence shift to the applicant. *Rijckaert*, 9 F.3d at 1532, 28 USPQ2d at 1956. When the references cited by the examiner fail to establish

a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988)." See *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995).

In order to establish a *prima facie* case of obviousness, the rejection must demonstrate that (1) the cited references teach all the claimed elements; (2) there is a suggestion or motivation in the prior art to modify or combine the reference teachings; and (3) there is a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). As explained below, Applicants submit that the cited reference does not teach all the claimed elements and fails to provide a basis for one of skill to reasonably expect that the disclosed compounds would be useful in treating anxiety, much less to increase ion flow through KCNQ potassium channels.

Gaster Fails to Explicitly or Inherently Teach a Method of Reducing Anxiety

The Examiner asserts that the aryl carbamoyl compounds of Gaster "are used to treat anxiety" and, therefore, inherently increase ion flow through KCNQ potassium channels as recited in claims 45-82. See page 4, lines 14-24 of Examiner's Office Action mailed September 26, 2003. Applicants respectfully disagree with the Examiner's assertion that the aryl carbamoyl compounds of Gaster "are used to treat anxiety." Furthermore, there is no evidence that the compounds inherently increase ion flow through KCNQ potassium channels. Applicants respectfully note that it is likely anxiety is caused by multiple mechanisms in addition to increasing ion flow through KCNQ potassium channels. Therefore, some compounds that are used to treat anxiety, including currently marketed medication, do not act as KCNQ openers.

The MPEP states: "The fact that a certain result or characteristic ***may*** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." See MPEP §2112 (emphasis in original), quoting *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." See MPEP §2112, quoting *In re Robertson* 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Furthermore, "[i]n relying upon a theory of inherency, the examiner must provide a basis in fact and/or technical

reasoning to reasonably support the determination that the allegedly inherent characteristic ***necessarily*** flows from the teachings of the applied prior art." See MPEP §2112 (emphasis in original), quoting *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

Here, Gaster provides no evidence that the disclosed aryl carbamoyl compounds actually reduce anxiety, much less through increasing ion flow through KCNQ potassium channels. Rather, Gaster merely discloses that "certain compounds of the invention exhibit $5HT_{2B}$ antagonist activity." See column 1, lines 20-21. Applicants acknowledge Gaster's statement that $5HT_{2B}$ antagonists "are believed to be of ***potential*** use in the treatment of CNS disorders, such as anxiety . . . ." See column 1, lines 21-23. However, Gaster never states that the disclosed aryl carbamoyl compounds are, in fact, able to treat anxiety. Moreover, no examples are provided in which any of the disclosed aryl carbamoyl compounds are shown to exhibit anxiety reducing characteristics. Therefore, one of skill in the art, after reading Gaster, would conclude that aryl carbamoyl compounds ***may*** be useful in the treatment of anxiety. Because the aryl carbamoyl compounds are not ***necessarily*** capable of reducing anxiety, inherency cannot be sufficiently established. See MPEP §2112, quoting *Ex parte Levy* and *In re Rijckaert*.

Assuming, arguendo, that the disclosed aryl carbamoyl compounds are capable of reducing anxiety, Applicants submit that there is no basis in fact and/or technical reasoning to reasonably support the determination that the aryl carbamoyl compounds ***necessarily*** increase ion flow through KCNQ potassium channels. See MPEP §2112, quoting *Ex parte Levy*. Applicants respectfully note that it is likely anxiety is caused by multiple mechanisms. Therefore, not all methods of reducing anxiety would be expected to work by increasing ion flow through a KCNQ potassium channel.

The Examiner has provided no basis or reasoning to support the assertion that a compound that reduces anxiety by antagonizing $5HT_{2B}$ receptors necessarily increases ion flow through KCNQ potassium channels. Nor is such basis or reasoning provided in Gaster or in Applicants' disclosure. Therefore, Applicants request that the Examiner provide a basis and/or

reasoning to conclude that the aryl carbamoyl compounds ***necessarily*** increase ion flow through KCNQ potassium channels or withdraw the rejection.

Gaster Fails to Provide a Basis for One of Skill to Reasonably Expect that the Aryl Carbamoyl Compounds would Increase Ion Flow Through KCNQ potassium channels

Even assuming, *arguendo*, that Gaster explicitly or inherently teaches a method of reducing anxiety, Applicants submit that one skilled in the art would not reasonably expect the aryl carbamoyl compounds of Gaster to increase ion flow through KCNQ potassium channels. $5HT_{2C}$ receptor antagonism is the only reported activity for these aryl carbamoyl compounds. One skilled in the art would immediately recognize that $5HT_{2c}$ receptors radically differ in structure and function from KCNQ potassium channels. Therefore, there is no reason for one of skilled in the art to conclude, *a priori*, that the $5HT_{2C}$ receptor antagonists disclosed by Gaster would function to open KCNQ channels. To find otherwise requires the exercise of impermissible hindsight reconstruction of the prior art. See *W.L. Gore & Associates Inc. v. Garlock Inc.*, 220 USPQ 303, 313 (Fed. Cir. 1983) (stating, "[t]o imbue one of ordinary skill in the art with knowledge of the invention in suit...is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher").

$5HT_{2C}$ receptors belong to the class A or rhodopsin-like G-protein-coupled receptors (GPCRs), a seven-transmembrane domain protein family. In response to chemical or physical external stimuli, GPCRs undergo a conformational change directly leading to the activation of heterotrimeric G-proteins and other intracellular signaling mediators. By contrast, KCNQ channels do ***not*** belong to the GPCR family. Rather, KCNQ channels are composed of KCNQ subunits that are members of the Kv superfamily of potassium channel monomers. The KCNQ subunits form pores thereby allowing ions to pass in a voltage dependent manner, which does not directly lead to activation of heterotrimeric G-proteins. Because of the divergent structure and function of $5HT_{2C}$ receptors and KCNQ channels, there is no reason to expect a $5HT_{2C}$ receptor antagonist to increase ion flow through a KCNQ potassium channel.

Applicants further submit that one of skill would not expect to successfully use these $5HT_{2B}$ antagonists in the treatment anxiety. The fact that Gaster mentions their potential use for treating anxiety might tempt one skilled in the art to test the compounds, but this meager statement of possibility would certainly not provide a reasonable expectation of success. The Federal Circuit has stated that "'[o]bvious to try' has long been held not to constitute obviousness." *In re Deuel*, 51 F.3d 1552, 1559 (Fed.Cir. 1995). Therefore, Applicants submit that Gaster fails to provide a reasonable expectation of successfully treating anxiety with the disclosed aryl carbamoyl $5HT_{2C}$ receptor antagonists.

Because one of skill in the art would have no reasonable expectation of successfully using the $5HT_{2C}$ receptor antagonists of Gaster to treat anxiety or increase ion flow through KCNQ potassium channels, Applicants respectfully request withdrawal of the rejection.

Double Patenting Rejection

The Examiner has rejected claims 45-57 under the judicially created obviousness-type double patenting as allegedly unpatentable over claims 46-67 of McNaughton-Smith et al., U.S. Patent No. 6,593,349 (hereinafter referred to as the '349 patent). Claims 45-82 stand rejected under the judicially created obviousness-type double patenting as allegedly unpatentable over claims 46-67 of McNaughton-Smith et al., U.S. Patent No. 6,593,349 in view of Gaster et al., U.S. Patent No. 6,235,758.

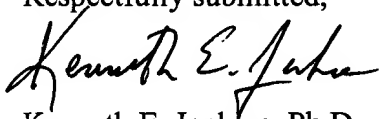
A terminal disclaimer will be filed in accordance with 37 CFR §1.321, should the claims be deemed otherwise allowable. Until such time, Applicants request that the rejection be held in abeyance.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Kenneth E. Jenkins, Ph.D.
Reg. No. 51,846

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
KEJ:kej
60112590 v1